

# Study Protocol of Endometrial scratching in egg donation cycles: The ENDOSCRATCH Trial (NCT03108157)

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## Abstract

The effects of endometrial scratching (ES) on embryo implantation have been studied for many years now. Several studies have shown better outcomes when it was applied to patients undergoing IUI and IVF, but many others have not been able to find such differences. When it comes to cycles with donor eggs, evidence is scarce.

Our aim in this trial is to determine if ES would be useful for those patients undergoing IVF cycles with donor eggs, since cycles would be much more homogeneous in terms of embryo quality and endometrial preparation.

## Key words

Endometrial scratching, endometrial scratch, recurrent implantation failure, egg donation, hysteroscopy, endometrial receptivity.

## Introduction

Embryo implantation remains one of the main deficits in assisted reproduction. Despite the improvements in reproductive medicine that have led to increasing pregnancy rates in the last few years, the implantation process is still barely known.

Many studies have tried to find ways to improve embryo implantation through different strategies: different protocols for controlled ovarian stimulation and endometrial preparation, embryo selection by time-lapse evaluation and preimplantational genetic testing and endometrial genetic assessment for implantation potential (Simon et al. 2014)

Endometrial scratching (ES) has been proposed to improve the embryo-endometrium dialogue by the effects of different cytokines and growth factors (Cakmak et al 2011, Taylor et al. 2011) involved in an acute endometrial inflammatory process, enhancement of new vascularization and decidualization (Gnainsky et al 2010), improving the endometrial

maturation (Nastri et al 2015), and promoting the endometrial gene expression that may lead to a better synchrony between the embryo and the endometrium (Kalma et al 2009).

Some authors (Lensen et al 2014) have studied the effects of ES in intrauterine insemination cycles or in spontaneous conception cycles. However, most of these studies are retrospective, based on heterogeneous populations, with ES performed at different moments and with a low number of patients. Senocak et al (2017) found a better clinical pregnancy rate and ongoing pregnancy rate when ES was performed the cycle prior to the IUI (OR 2,29, 95%IC:1.14-5.05), but a previous meta-analysis by Vitagliano et al (2017) had found similar differences when it was performed during the stimulation cycle (OR 2,04,  $p < 0,00001$ ).

Regarding IVF, several studies have tried to determine whether an endometrial injury (endometrial scratching: ES) performed in the cycle preceding the embryo transfer could enhance embryo implantation. Barach et al. (2003) reported for the first time an increase in pregnancy rates in patients that had undergone an ES before the IVF cycle.

Most of the studies have tried to determine ES effects after controlled ovarian stimulation (COS) and have found an increase in pregnancy rates (Barach et al 2003, Raziel et al 2007, Zhou et al 2008) but many others have been unable to find such differences (Lensen et al. 2019, Frantz et al. 2019, Yeung et al. 2014, Eskew et al 2018, Baum et al. 2012). The main limitation for all these studies is the low number of patients included, as well as heterogeneity among populations when considering previous implantation failures. In addition, most of them are underpowered observational studies with differences in timing and procedure for the ES. A systematic review by Potdar et al (2012) which included 7 studies in 2062 patients found a three-fold difference in pregnancy rates in those patients that received the ES. Those results were validated some time later by a Cochrane Review (2012).

Despite all these studies after COS, there is low evidence of the possible effect of this endometrial scratching when performed in patients that will receive embryos from donor eggs, and who haven't undergone an ovarian stimulation (Dain et al 2014).

When comparing patients in egg donation cycles, we find two main differences from all other studies in IVF treatments. The first one is that embryo quality is maximal, since all embryos come from donor eggs, avoiding then the confusion factor of embryo quality according to maternal issues (age, BMI, polycystic ovaries, low ovarian reserve...). The second one is that all patients receive hormonal replacement therapy, with an homogeneous preparation of

the endometrium, avoiding then the different hormonal environments caused by uneven responses to controlled ovarian stimulation in IVF.

Our main purpose is to determine whether a mild endometrial injury (endometrial scratching) performed the cycle prior to the embryo transfer can help the synchronization between the embryo and the endometrium and thus enhance the implantation process in egg donation cycles.

## **Objective**

The main objective of this trial is to determine if there are differences in ongoing pregnancy rates after egg donation treatments, when an endometrial scratching is performed versus those patients who don't receive it.

## **Hypothesis**

Patients that receive an endometrial scratching during the previous cycle to the embryo transfer, have an increased endometrial receptivity and thus higher pregnancy rates.

We have designed the statistical analysis to find a 15% difference in pregnancy rates between the two groups.

## **Methods**

### ***Study Design***

This is a prospective randomized controlled trial fully conducted at Procreatec International Fertility Clinic in Madrid, starting January 2017.

Those patients undergoing an egg donation cycle that meet the inclusion criteria will be invited to participate in this study. We will obtain the informed consent from all patients, according to the Ethics Committee approval.

Once patients have accepted the study and signed the informed consent, they will be allocated to each treatment group, according to the randomization protocol. Those patients included in Group A will undergo an endometrial scratching the cycle prior to the embryo transfer. Those patients assigned to Group B will follow the conventional protocol without endometrial scratch.

All information regarding patients, assignment, treatment protocol and results will be

included in our database to conduct the statistical analysis.

### ***Study Setting***

#### **Study Population**

All patients undergoing egg donation treatments at ProcreaTec Fertility Clinic are eligible for the study.

Patients will be included if they meet the following inclusion criteria:

- Patients undergoing an IVF protocol with donor eggs
- Normal uterine cavity
- Patients with endometrial polyps can be included as long as polypectomy is performed at least two months before the treatment is done.

Patients will be excluded if:

- There is a severe male factor (less than 2 million sperms per ml)
- They have uterine anomalies such as uterine fibroids that impact the cavity, Mullerian malformations or severe adenomyosis.

#### **Sample size calculation**

Average pregnancy rates after embryo transfer in egg donation cycles is 60% in our center. We estimated that a total of 332 patients will be necessary to include to detect a 15% difference in pregnancy rates between the two groups, with 80% statistical power. Considering a 5% dropout rate, we will include 176 patients per study arm, 352 patients in total.

#### **Recruitment, consent and randomization**

Patients starting egg donation cycles that fulfill inclusion criteria will be offered to participate. If they agree, IC should be signed and they will be assigned to a treatment group following the randomization chart obtained from randomization.com.

#### **Study Procedure**

Randomized patients will receive their treatment protocols once the egg donor has been proposed and accepted.

Group A patients will receive an endometrial biopsy-scratching before they start the

endometrial preparation, during the luteal phase of the previous cycle.

Group B patients will start the conventional treatment protocol without endometrial biopsy.

### ***Follow up***

We will follow the development of the cycle, from the moment the donor is assigned until we have a pregnancy test, and if positive, then the ultrasound confirmation for pregnancy.

### ***Ethical issues and authorization***

This study will be conducted after the authorization of the Ethical Committee of Princesa Hospital in Madrid.

Clinical data will be treated confidentially following the Spanish protection data law (Ley Orgánica 15/1999 de 13 de diciembre, de Protección de Datos de Carácter Personal).

### ***Data collection and analysis***

All data will be collected from patients included in the trial, from ProcreaTec clinical records, according to the information required in the data collection form.

Statistical analysis will be done using STATA 13 for Windows (StataCorp LP, Texas). Qualitative variables will be analyzed using central statistics and standard deviation. Qualitative variables will be described using frequency distribution. Association among variables will be explored by statistical tests according to their nature and distribution.

### ***Study variables***

a) Independent variable:

Scratching vs no scratching during the luteal phase of the previous cycle.

b) Dependent variable:

Positive Clinical pregnancy or not.

### ***Study co-variables***

a) Sociodemographic:

- Race
- Maternal age

- BMI (kg/m<sup>2</sup>)
  - Smoking habits
- b) Reproductive history:
- Previous pregnancies: term, biochemical miscarriages, clinical miscarriages, ectopic pregnancies, stillbirths.
  - Previous embryo transfers from own eggs.
  - Previous embryo transfers from donor eggs.
- c) Treatment protocol:
- Number of days of estrogen therapy before the start of progesterone.
  - Type, dose and administration of estrogens.
  - Endometrial thickness before the start of progesterone.
  - Estradiol blood levels the day of the start of progesterone (mcg/ml)
  - Progesterone blood levels the day of the start of progesterone (ng/l)
  - Type, dose and administration of progesterone.
- d) Laboratory details:
- Number of eggs obtained from the donor.
  - Age of the donor
  - Sperm quality the fertilization day.
  - Number of embryos obtained.
  - Number of embryos available the day of the embryo transfer.
  - Number of transferred embryos
  - Quality of transferred embryos
  - Results of pregnancy test: positive-negative.
  - Implantation rate.
  - Clinical pregnancy rate: gestational sac observed by US at 5-6 weeks of pregnancy.
  - Biochemical Miscarriage rate.
  - Clinical Miscarriage rate.
  - Live birth rate.
  - Obstetrical complications.

## Discussion

Embryo implantation is the limiting factor for pregnancy. It occurs in about 30% of all conceptions and it remains a defy for all assisted reproduction treatments. Patients and specialists have a major concern when the treatment fails and many times the only unknown step is the embryo-endometrium crosstalk.

Endometrial scratching (ES) has been proposed by several authors as a simple, easy and cost-effective technique to improve the endometrial receptivity to the embryo, helping the synchronization of endometrium and embryo.

This randomized controlled trial will try to clarify whether the ES can improve pregnancy rates in egg donation treatments, being thus beneficial for those patients, or if there is an specific group of patients where it might be specially indicated. The main strength for this study will be the number of patients recruited as well as the homogeneous stimulation protocols and embryo quality.